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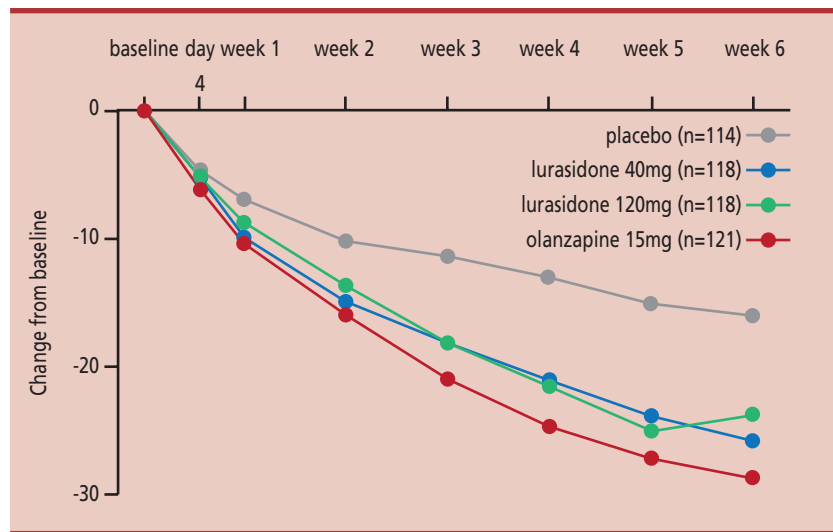
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# Lurasidone: new development for the treatment of psychosis

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Although we have had efficacious medications for both schizophrenia and bipolar disorder for over half a century, there remains a clear need for more effective and better-tolerated treatments for both conditions. Current antipsychotics often have troubling side-effect profiles particularly with respect to weight gain and cardiometabolic parameters. These drawbacks also extend to treatment of mania and there are very few evidence-based treatments for the depressed phases of bipolar disorder. The introduction of a novel treatment with a potentially better risk-to-benefit profile is therefore welcome.

Lurasidone is a novel second-generation antipsychotic.<sup>1</sup> Like other newer antipsychotics, it is an antagonist at dopamine D<sub>2</sub> and 5HT<sub>2A</sub> receptors but it has less affinity for alpha<sub>1</sub> receptors than other second-generation antipsychotics and negligible affinity for histamine H<sub>1</sub> and muscarinic receptors. Unusually, it also has high affinity for 5HT<sub>1A</sub> receptors, which are believed to be important for anxiolytic and antidepressant activity and 5HT<sub>7</sub> receptors, which appear to have a role in learning and memory.



**Figure 1.** Change from baseline in PANSS total score for lurasidone 40 or 120mg vs placebo with olanzapine as active control (PEARL2)<sup>3</sup>

These pharmacological characteristics suggest that lurasidone, in addition to its efficacy as an antipsychotic, has the potential to improve cognitive deficits and depressive symptoms associated with schizophrenia and is likely to be associated with a low risk of weight gain and metabolic dysfunction.

## CLINICAL TRIALS EFFICACY

### Schizophrenia

The Program to Evaluate the Antipsychotic Response to Lurasidone (PEARL) comprised three phase 3 randomised trials of similar design.<sup>2-6</sup> Patients with acute exacerbation of schizophrenia and Positive and Negative Syndrome Scale (PANSS) total score  $\geq 80$  were randomised to treatment with lurasidone 40, 80 or 120mg daily or placebo (PEARL1). Non-comparative active controls were

included in PEARL2 (olanzapine 15mg daily)<sup>3</sup> and PEARL3 (modified-release quetiapine 600mg daily).<sup>5</sup> All consisted of a fixed-dose double-blind phase of six weeks followed by a flexible-dose extension phase. The primary end-point in each study was the change from baseline in the PANSS total score; secondary end-points included the PANSS positive and negative scores and the Clinical Global Impression-Severity (CGI-S) score.

In PEARL1 (n=500), lurasidone 80mg daily significantly improved total PANSS and CGI-S scores compared with placebo at six weeks, though neither the lower or higher dose did so.<sup>2</sup> Positive symptoms were significantly improved at doses of 80 and 120mg daily but not 40mg daily, and there was no difference between lurasidone and placebo in change in PANSS negative symptom score or in symptoms

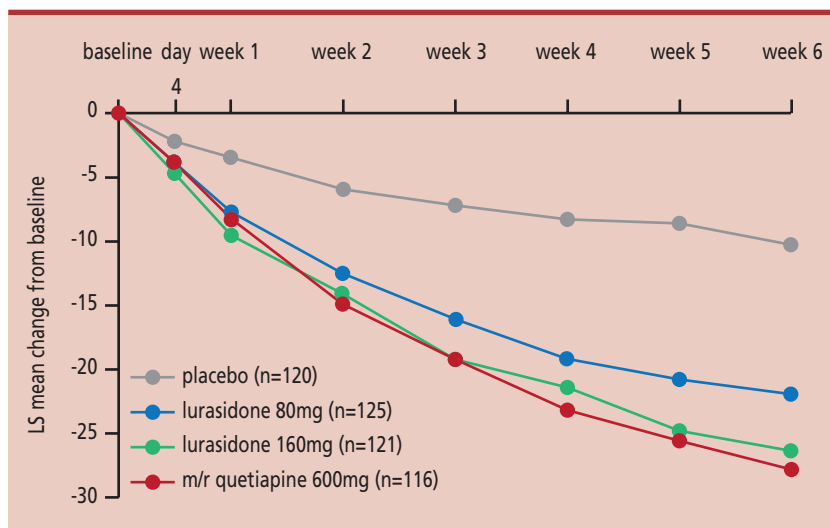
of depression. The results of the PEARL1 extension study are not yet available.

In PEARL2 (n=478), lurasidone 40 or 120mg daily both significantly improved PANSS total score, PANSS positive and negative scores and CGI-S score compared with placebo after six weeks (see Figure 1). Significant separation was evident at the end of the first week.<sup>3</sup> Olanzapine 15mg, as an active control, was also superior to placebo.

In PEARL3 (n=488), patients were randomised to treatment with lurasidone 80 or 160mg daily, placebo or modified-release (m/r) quetiapine 600mg daily.<sup>5</sup> Both doses of lurasidone significantly improved PANSS total, positive and negative scores and CGI-S score by six weeks compared with placebo, with similar efficacy as quetiapine (see Figure 2).

Lurasidone also significantly improved depression scores (Montgomery-Asberg Depression Rating Scale, MADRS), negative symptoms (Negative Symptom Assessment Scale) and somnolence (Epworth scale) compared with placebo.

Patients who responded to treatment with lurasidone or quetiapine ( $\geq 20\%$  reduction in PANSS total score and CGI-S  $\leq 4$  at six weeks) were eligible to enter a noninferiority trial to compare their efficacy in preventing relapse (n=292).<sup>6</sup> The initial blinding was maintained. The probability of relapse over 12 months was 24 per cent with lurasidone and 34 per cent with quetiapine, meeting the criterion for noninferiority. Lurasidone was also associated with a lower 12-month relapse rate (24 vs 34% with quetiapine), a lower rate of hospital admission (9.8 vs 23%) and a higher rate of remission (62 vs 46%).



**Figure 2.** Change from baseline in PANSS total score for lurasidone 80 or 160mg vs placebo with m/r quetiapine as active control (PEARL3)<sup>5</sup>

A recent meta-analysis comprehensively compared the efficacy of lurasidone to placebo and other antipsychotics commonly used to treat schizophrenia.<sup>7</sup> Lurasidone treatment produced a relatively small but significant improvement in symptoms of schizophrenia compared to placebo (standard mean difference 0.33). Lurasidone was, however, significantly less effective at treating symptoms of schizophrenia than clozapine, amisulpride, olanzapine, risperidone and paliperidone (Invega) and had similar efficacy profiles to haloperidol, quetiapine, chlorpromazine and asenapine (Sycrest).

#### Symptoms of depression in patients with schizophrenia

A *post-hoc* analysis of four six-week double-blind placebo-controlled trials that had included an assessment of depressive symptoms (n=1341) found that lurasidone 40–160mg daily significantly improved MADRS scores overall and in each subgroup defined by baseline symptom severity.<sup>8</sup> However, further analysis by dose

showed that only 80 and 160mg daily were statistically superior to placebo.

In patients with clinically significant depression at baseline (MADRS  $\geq 16$ ), the proportions of patients in remission at six weeks were 27% with placebo and 39 and 48% with lurasidone 80 and 160mg daily.

#### Cognitive function in patients with schizophrenia

Cognitive function was assessed in the PEARL3 trial.<sup>9</sup> There were no significant differences between lurasidone and placebo (or quetiapine vs placebo) at six weeks but after 32 weeks lurasidone improved cognitive function significantly more than quetiapine. This was independent of PANSS positive, PANSS negative or overall symptom reductions at weeks 6 and 32.

#### Bipolar I depression

Lurasidone has been evaluated in the treatment of bipolar I depression (baseline MADRS score  $\geq 20$ ) in two double-blind placebo-controlled trials.

In PREVAIL1 (n=346), lurasidone 20–120mg daily was added to treatment with either lithium or valproate.<sup>10</sup> After six weeks, lurasidone improved depressive symptoms significantly more than placebo (MADRS score: -17.1 *vs* -13.5 with placebo,  $p<0.01$ , effect size 0.30; CGI-bipolar depression severity rating: -2.0 *vs* -1.5 with placebo,  $p<0.01$  effect size 0.36), with secondary end-points demonstrating a reduction in disability (Sheehan Disability Scale total score -9.5 *vs* -7.0 with placebo;  $p\leq 0.01$ ).

PREVAIL2 randomised 505 patients to monotherapy with lurasidone 20–60mg daily or 80–120mg daily or placebo.<sup>11</sup> After six weeks, lurasidone improved depressive symptoms (MADRS score -15.4 for each dose *vs* -10.7 with placebo,  $p<0.001$ ; CGI-bipolar depression severity rating -1.8 and -1.7 *vs* -1.1 with placebo,  $p<0.001$ ), disability and quality-of-life scores compared with placebo, with no difference in outcomes between the doses.

#### ADVERSE EFFECTS

The commonest adverse events reported in clinical trials were dose-related akathisia (ranging from 11–12 per cent at 40mg daily to 23–24 per cent at 120mg daily), headache, somnolence, nausea and parkinsonism.<sup>2,3,5</sup> In one trial, lurasidone did not significantly affect glycaemic control or lipid levels compared with placebo.<sup>4,6</sup>

A recent meta-analysis<sup>7</sup> found that lurasidone treatment had no effects on weight gain or QTc interval prolongation compared to placebo in patients with schizophrenia and was significantly less likely to cause these effects than risperidone, quetiapine and olan-

zapine. Lurasidone treatment was associated with increased rates of sedation compared to placebo (odds ratio 2.45), similar to many other antipsychotics, but was significantly better than chlorpromazine and clozapine.

Lurasidone treatment had a small effect in increasing prolactin levels, and was significantly worse than aripiprazole or quetiapine, which had placebo level effects on prolactin levels.

Importantly, lurasidone was found to be one of the least well-tolerated antipsychotics with regard to extrapyramidal side-effects (odds ratio compared to placebo 2.45), and lurasidone treatment was associated with significantly higher rates of extrapyramidal side-effects than aripiprazole, quetiapine, olanzapine or clozapine.

Lurasidone is predominantly metabolised by hepatic CYP3A4 enzymes. It should not be co-administered with strong inhibitors or inducers of CYP3A4 and the dose should be limited to 40mg daily with a moderate CYP3A4 inhibitor such as diltiazem. No dose adjustment is required when lurasidone is taken with lithium.

#### POTENTIAL PLACE IN CLINICAL PRACTICE?

Lurasidone will offer a new treatment option for patients with schizophrenia and bipolar I depression; however, its role in the treatment of manic episodes of bipolar I disorder has yet to be evaluated. Significant benefits have been demonstrated for treating psychotic and depressive symptoms and lurasidone's lack of effect on weight gain or QTc-interval prolongation seems favourable.

The main adverse effect of note appears to be increased rates of extrapyramidal side-effects and we would suggest that clinicians

consider this when using lurasidone for patient populations who may be particularly likely to develop or who have previously not been able to tolerate these symptoms.

Overall, it seems likely that lurasidone will be carefully considered on its merits for inclusion into current treatment protocols for both schizophrenia and bipolar I depression.

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#### DECLARATION OF INTERESTS

Dr Stokes has none to declare. Professor Young has received payment for lectures and advisory boards for all major pharmaceutical companies with drugs used in affective disorders including Sunovion.